

*Lawrence Berkeley National Laboratory*



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**LBNL NANOHIGH**

## ***Cancer and aging: Rival demons?***

*Buck Institute for Age Research*



# **THANKS!**

## **Present lab members**

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Jean Philippe Coppe  
Albert Davalos  
Adam Freund  
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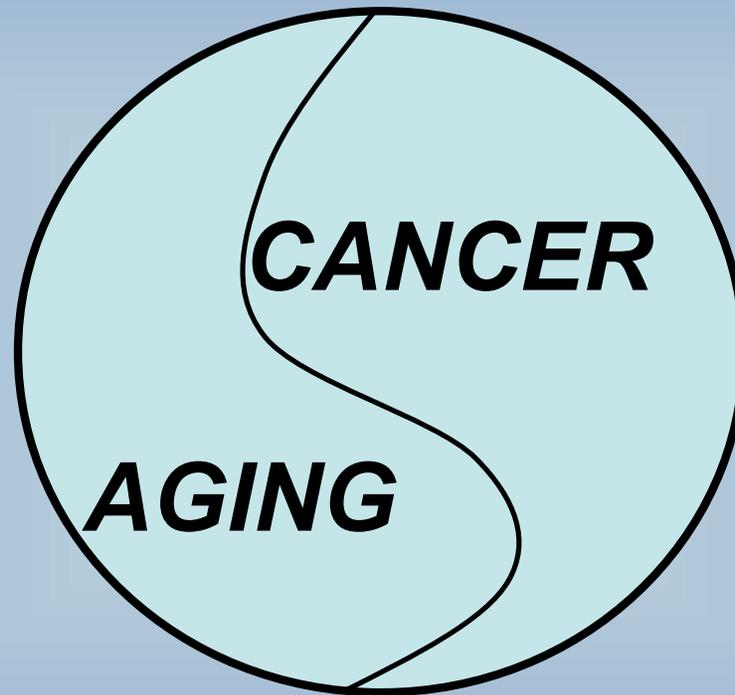
## **Past lab members**

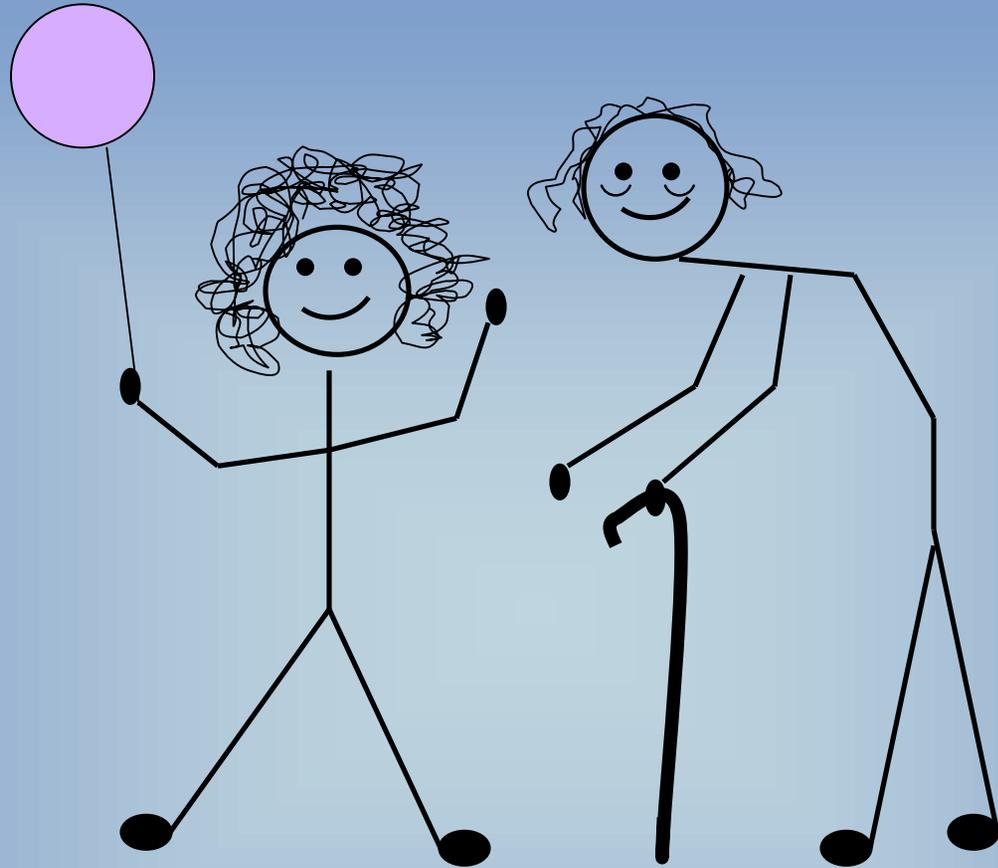
*Christian Beausejour (McGill U)  
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Shurong Huang (U WA)  
Patrick Kaminker (Celera)  
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*Aging and cancer are linked by the behavior of cells and forces of evolution*





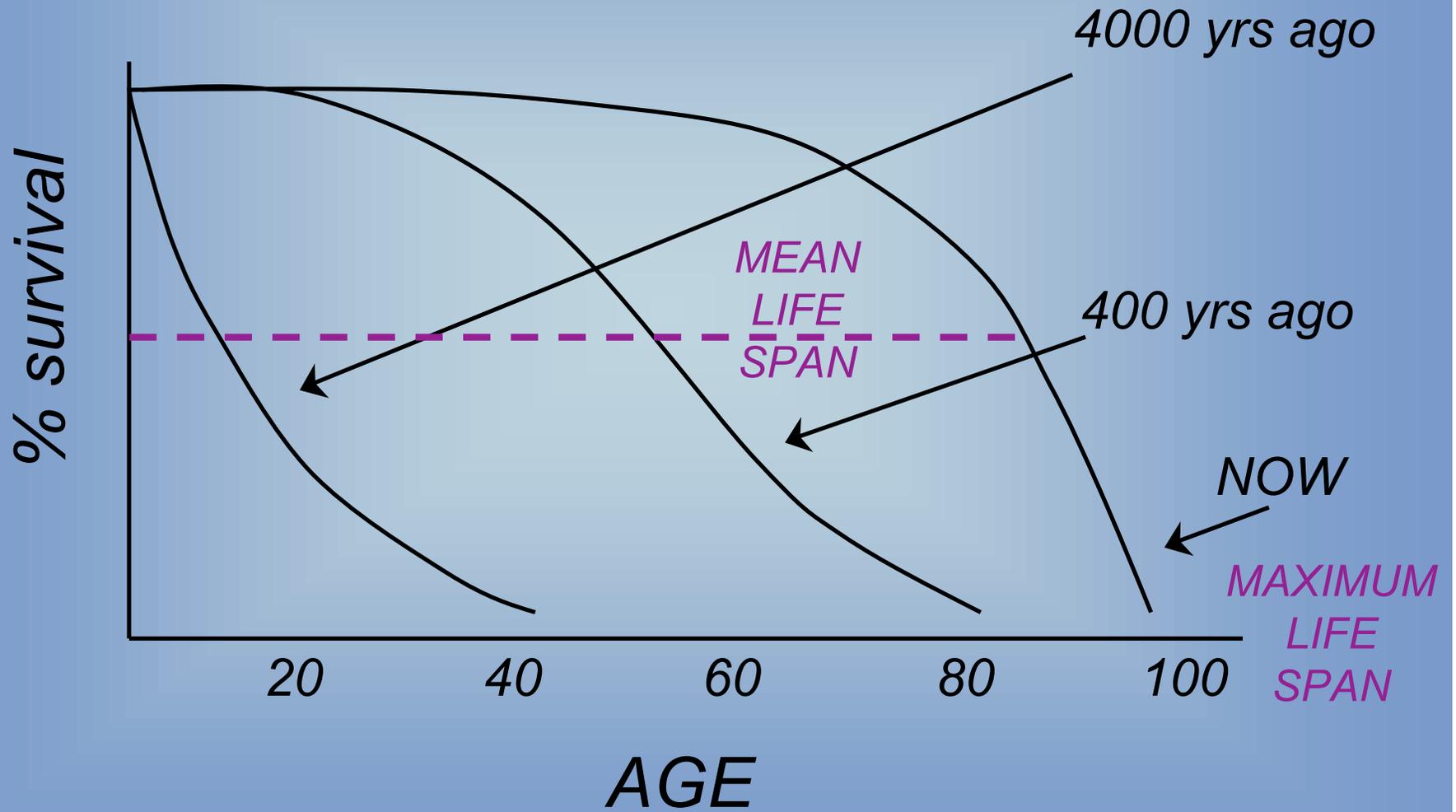
**What IS Aging?**

*Aging is a process*

*Aging is not disease per se*

*Aging occurs at the level of organisms,  
tissues, cells, and molecules*

# Aging vs Death (humans)





## What IS Aging?

*Aging is the process that changes a fit (young) organism into a less fit (old) organism*

## *Some basic characteristics of aging ...*

*Evolution has engineered a >100,000-fold difference in maximum life span among species!*



*Rate of aging is genetically controlled*

## *Some basic characteristics of aging ...*

*Calorie restriction:  
20-50% life span increase*

*Gene mutations:  
20->300% life span increase*

*Drugs:  
20-80% life span increase*

*Rate of aging within species is not 'fixed'  
(aging CAN be slowed!)*

*Some basic characteristics of aging ...*

*Interventions that slow aging  
have modest effects  
compared to what evolution  
has done*

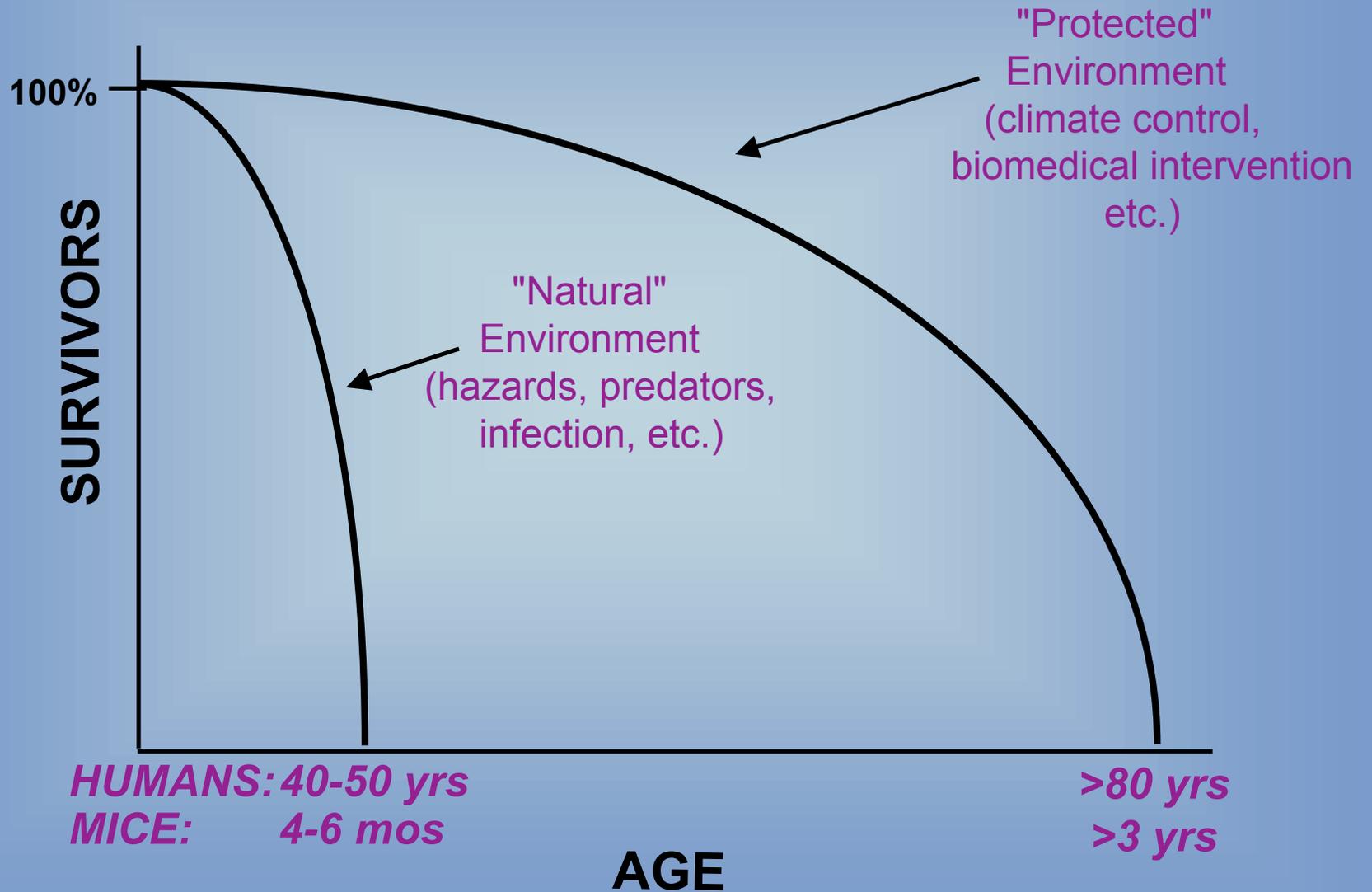
*Even the simplest organisms are complex;  
evolutionary changes are sequential, over  
long intervals, and often subtle*

*Evolution matters!*

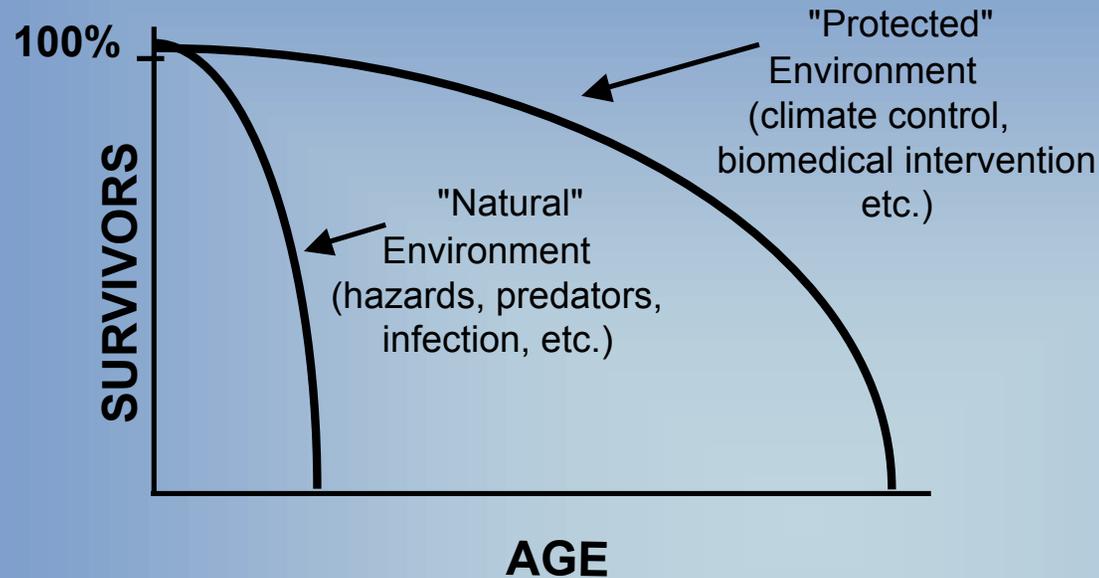
## *WHAT CAUSES AGING?*

*Aging is a consequence of the declining  
force of natural selection  
(evolution)  
with age*

# *Aging before cell phones .....*



# ***Aging is a consequence of the declining force of natural selection with age***



**Mutation Accumulation** ("*bad*" genes can persist)

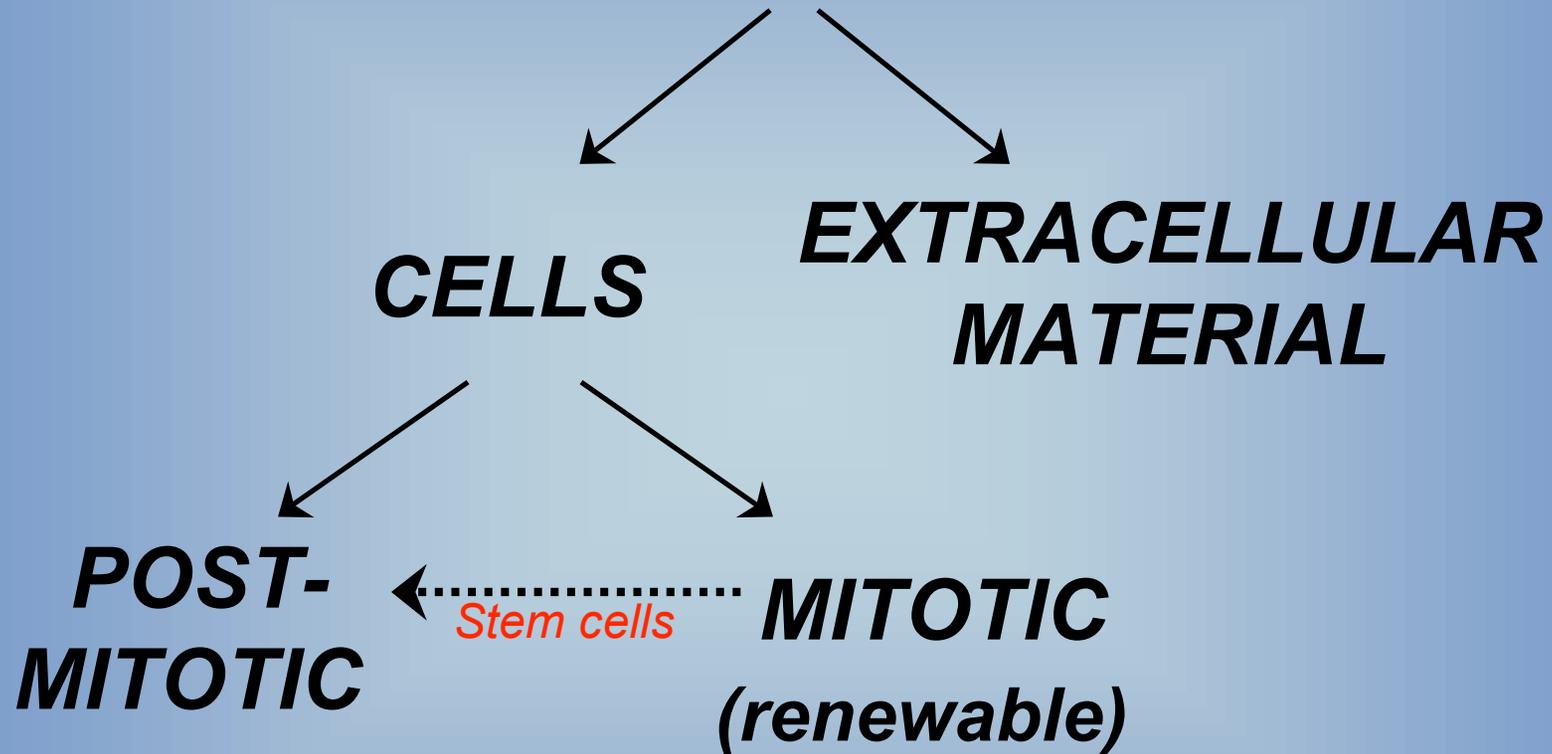
**Antagonistic Pleiotropy**

*(what's good when you're young can be bad when you're old)*

## *WHAT CAUSES AGING?*

*Aging occurs at the level of organisms,  
tissues, cells, and molecules*

# *A simple definition of complex organisms (like us)*

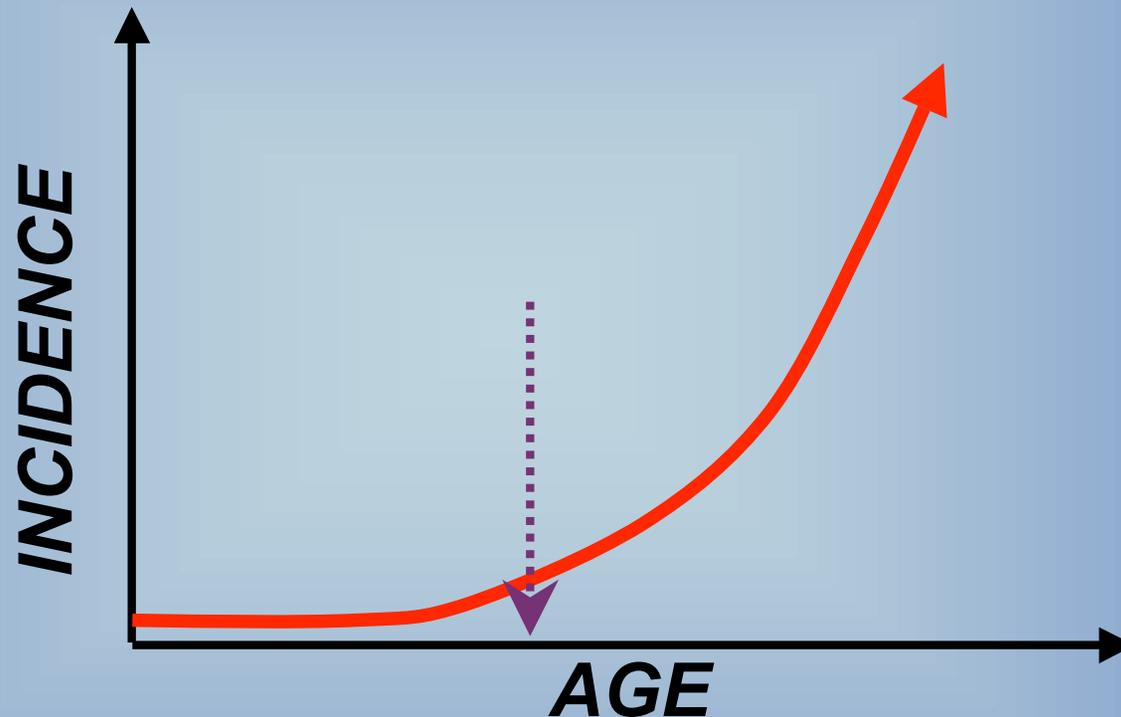


*Degenerative disease*

*Degenerative disease  
Cancer (hyperproliferative disease)*

# CANCER

*Cancer is an age-related disease*



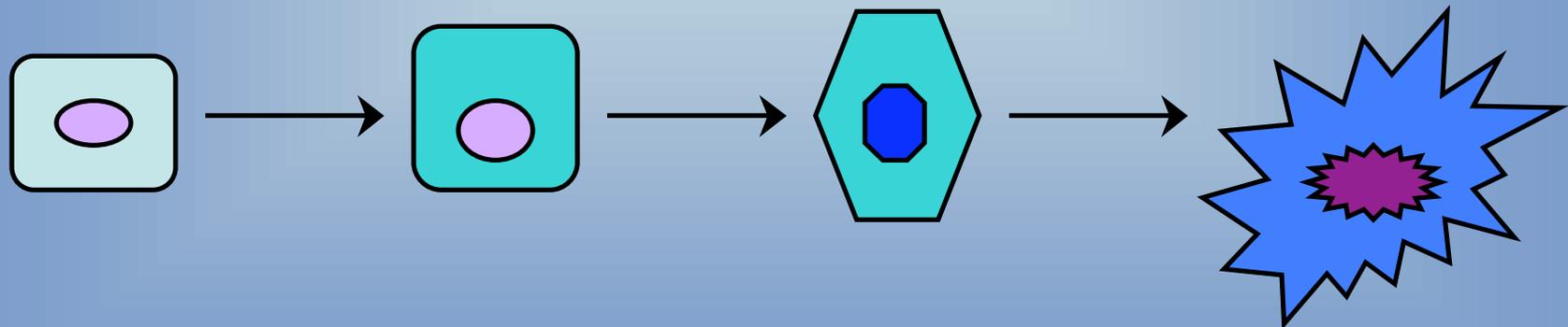
*Age is the largest single risk factor  
Incidence vs mortality  
Similar to other age-related diseases*

## ***What Is Cancer?***

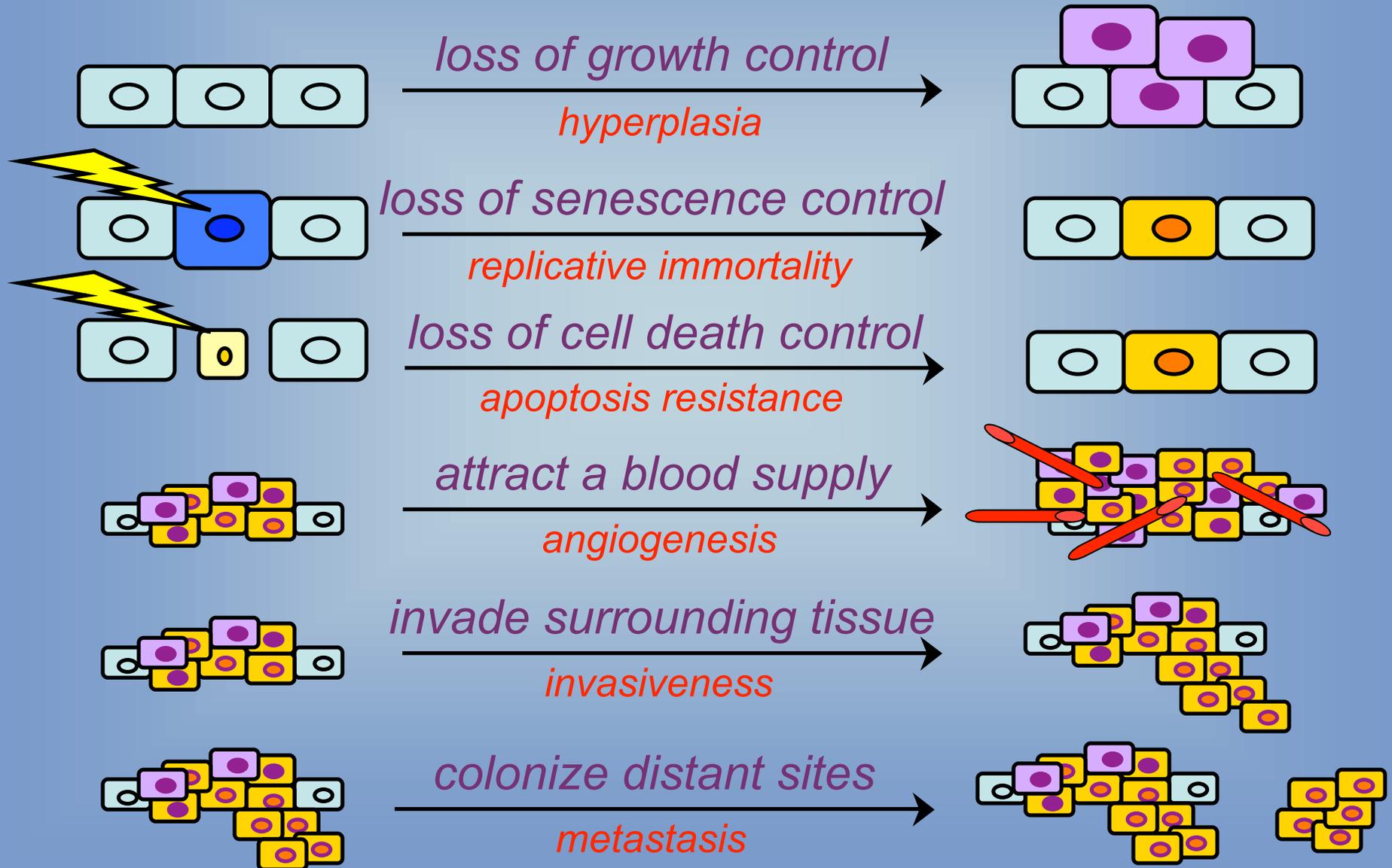
*Abnormal proliferation (growth) of cells  
that has high potential to kill the organism*

# ***Cancer is a disease of cells***

*Individual cells -- often a single cell --  
develop mutations -- many mutations --  
that give them properties of cancer cells*



# What makes a cell a cancerous (malignant)?



# ***What Causes Cancer?***

***Mutations, mutations, mutations ...***

**AND**

***A permissive tissue***

# ***Mutations, mutations, mutations ...***

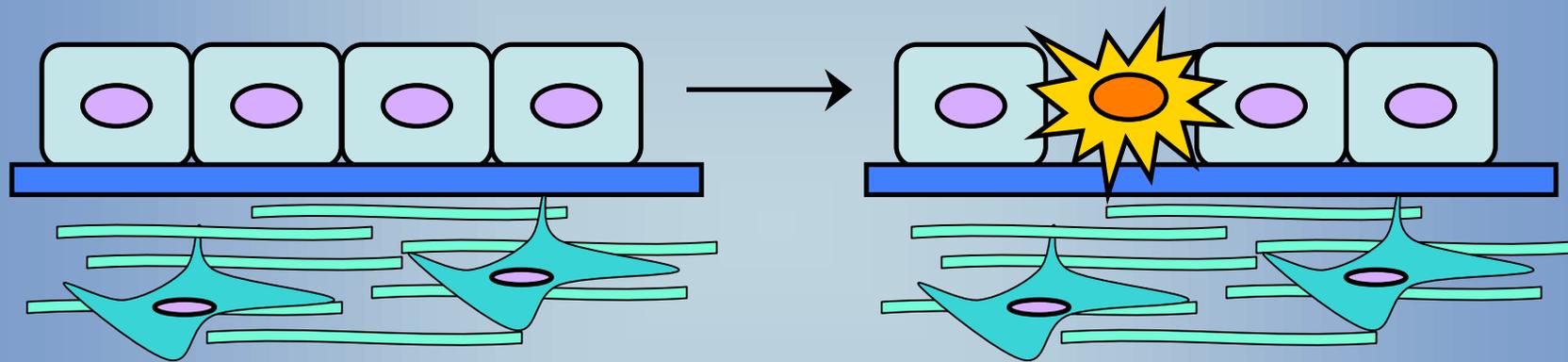
*Mitotic (dividing) cells are at the greatest risk for acquiring mutations  
(DNA synthesis is risky!)*

*Mutations begin to accumulate very early  
in life*

*Mutations increase as we age*

# *Tissue structure ...*

*Restrains mutant cells*



***TISSUE STRUCTURE  
DEGRADES WITH AGE***

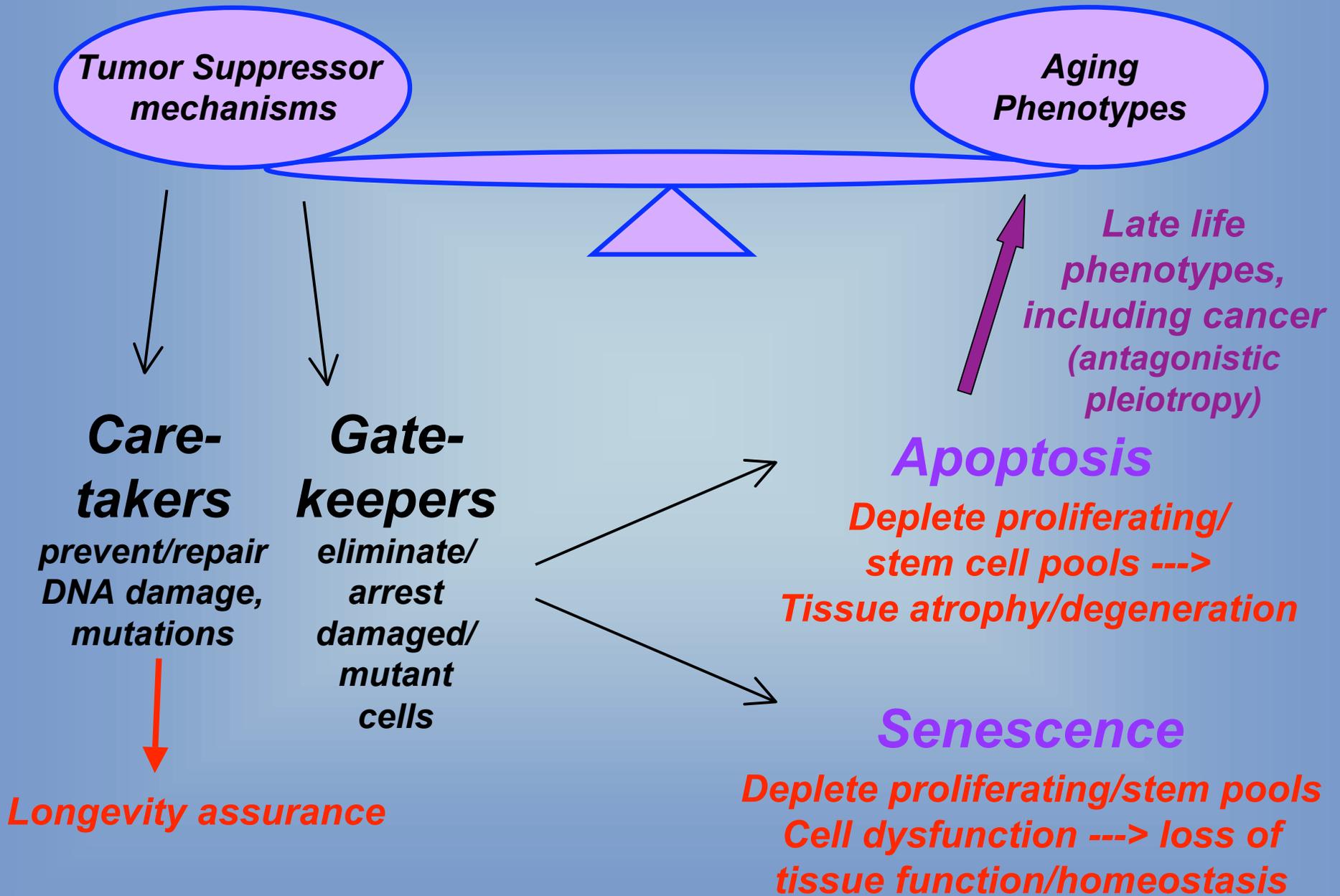
*If cells divide frequently in mitotic tissues,  
and mutations accumulate continually,  
and tissue structure degrades through life,  
why do we not get cancer more often?*

***Organisms with mitotic tissues  
had to evolve mechanisms  
to prevent cancer***

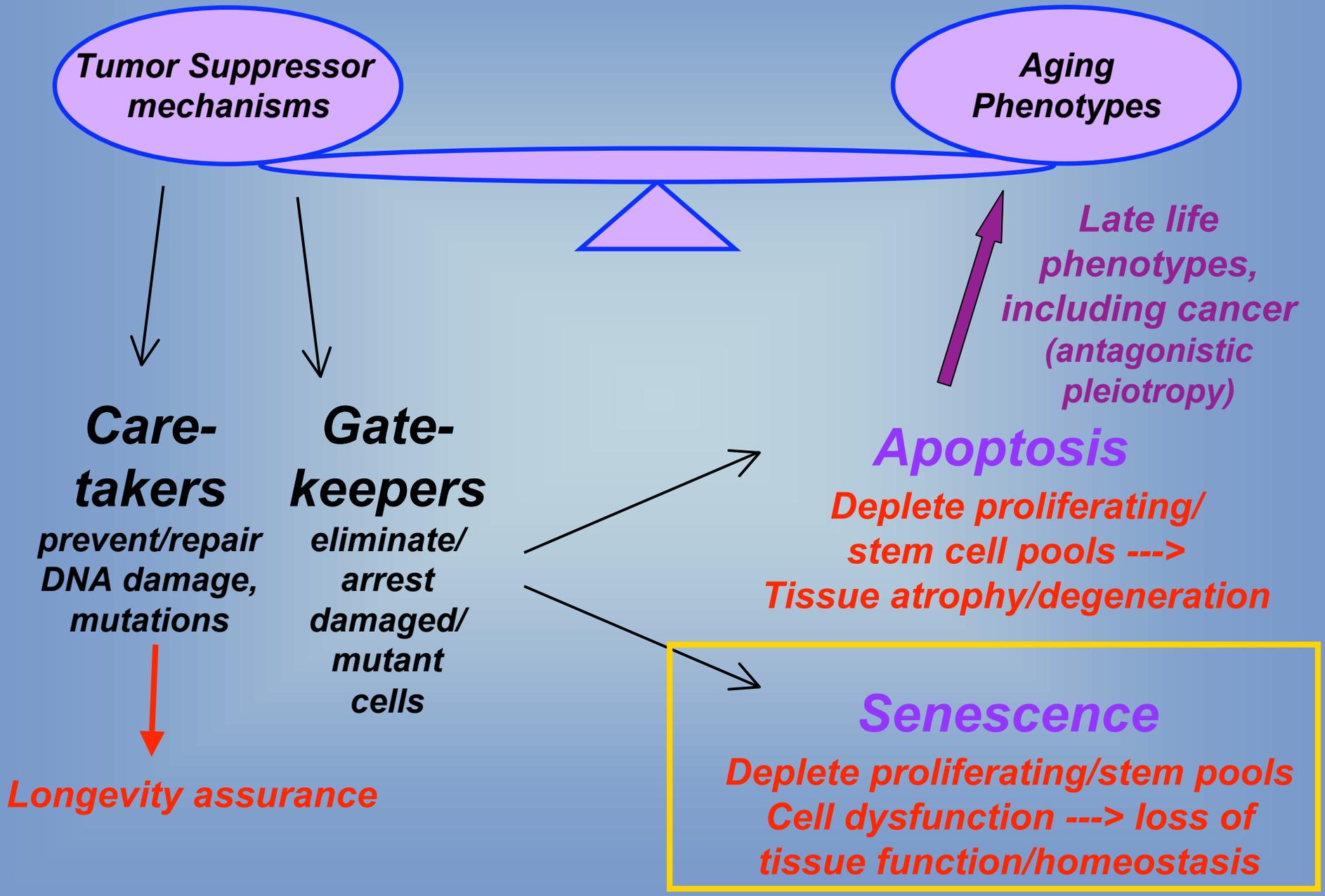


***Tumor Suppressor Mechanisms***

# Suppressing cancer costs -- aging



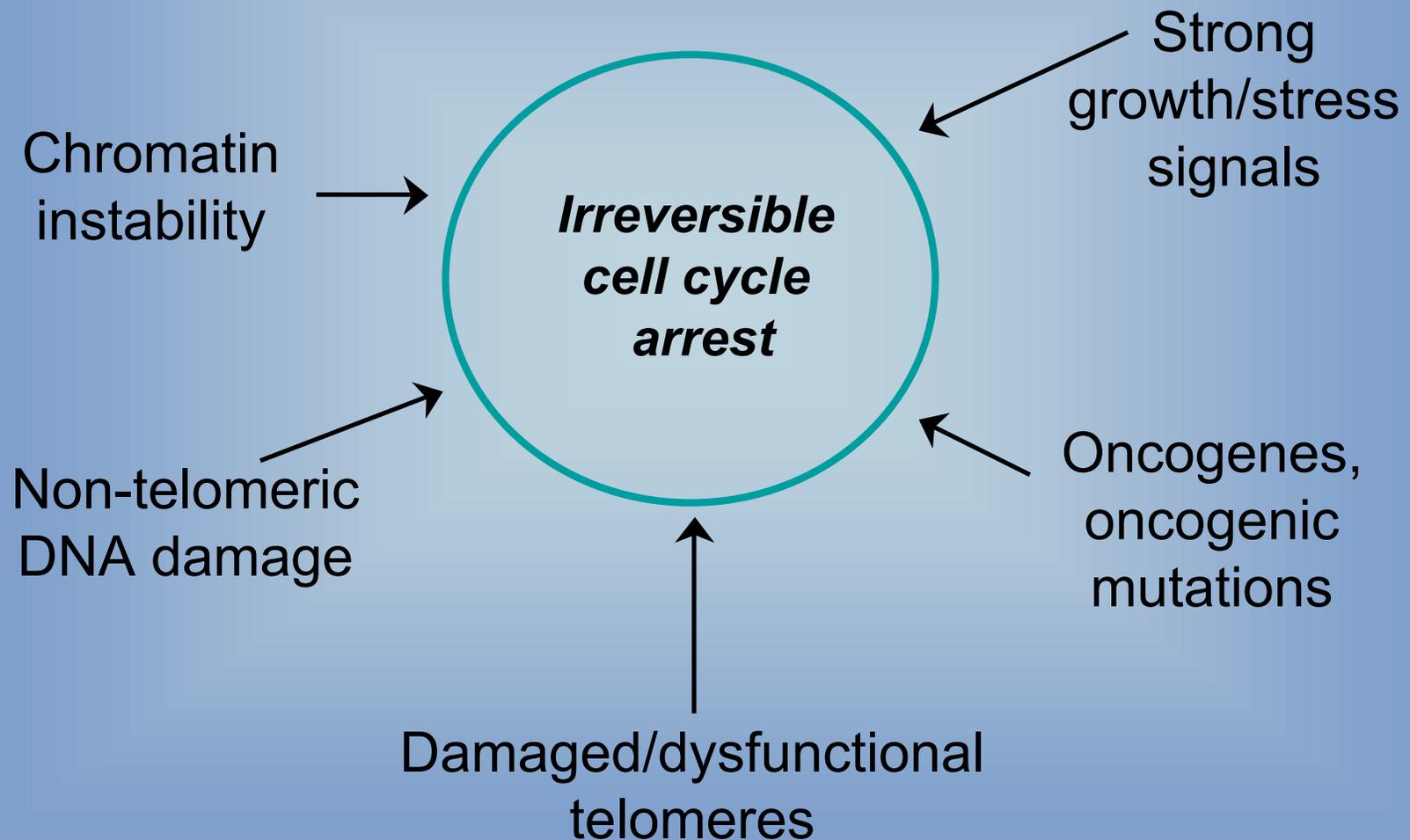
# Suppressing cancer costs -- aging



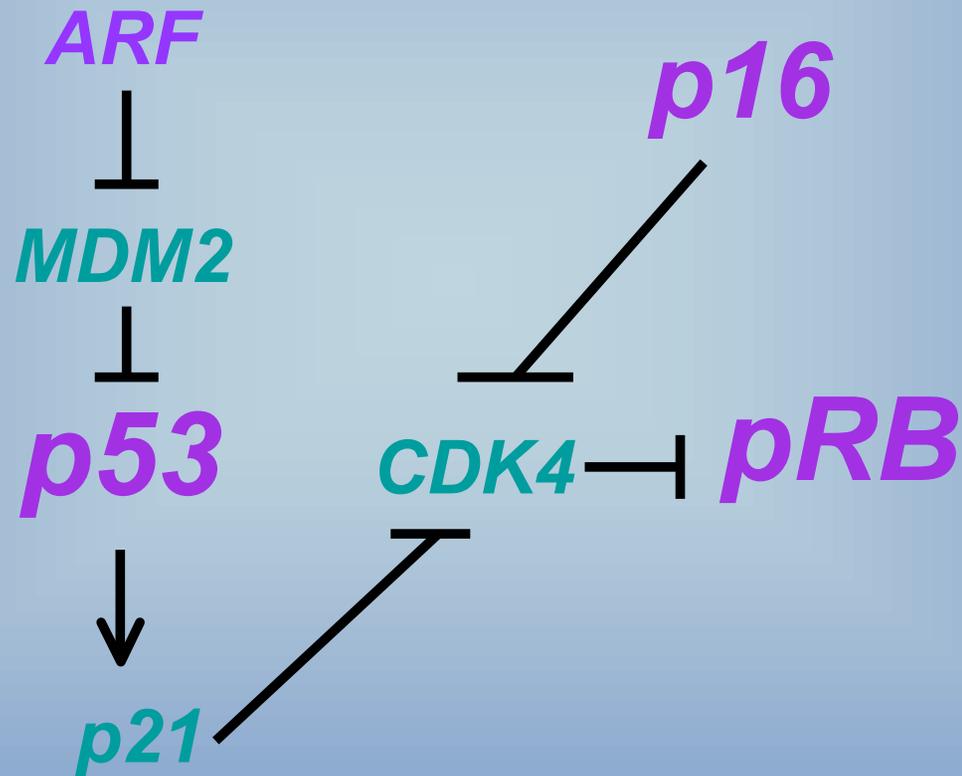
*Important characteristics of  
cellular senescence*

*Senescent cells lose the ability to divide,  
essentially irreversibly*

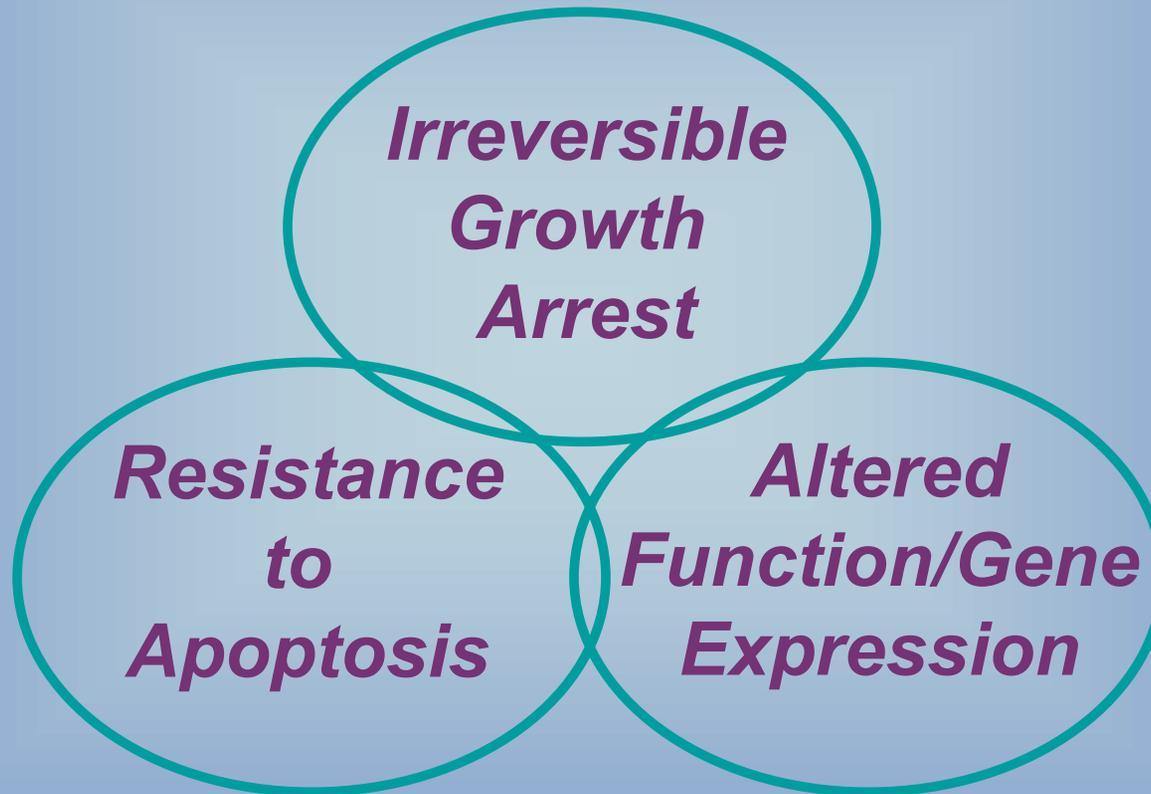
# *Cellular senescence is caused by stimuli that cause cancer*



*Cellular senescence is controlled by major tumor suppressor pathways*



# *The senescent phenotype is complex*

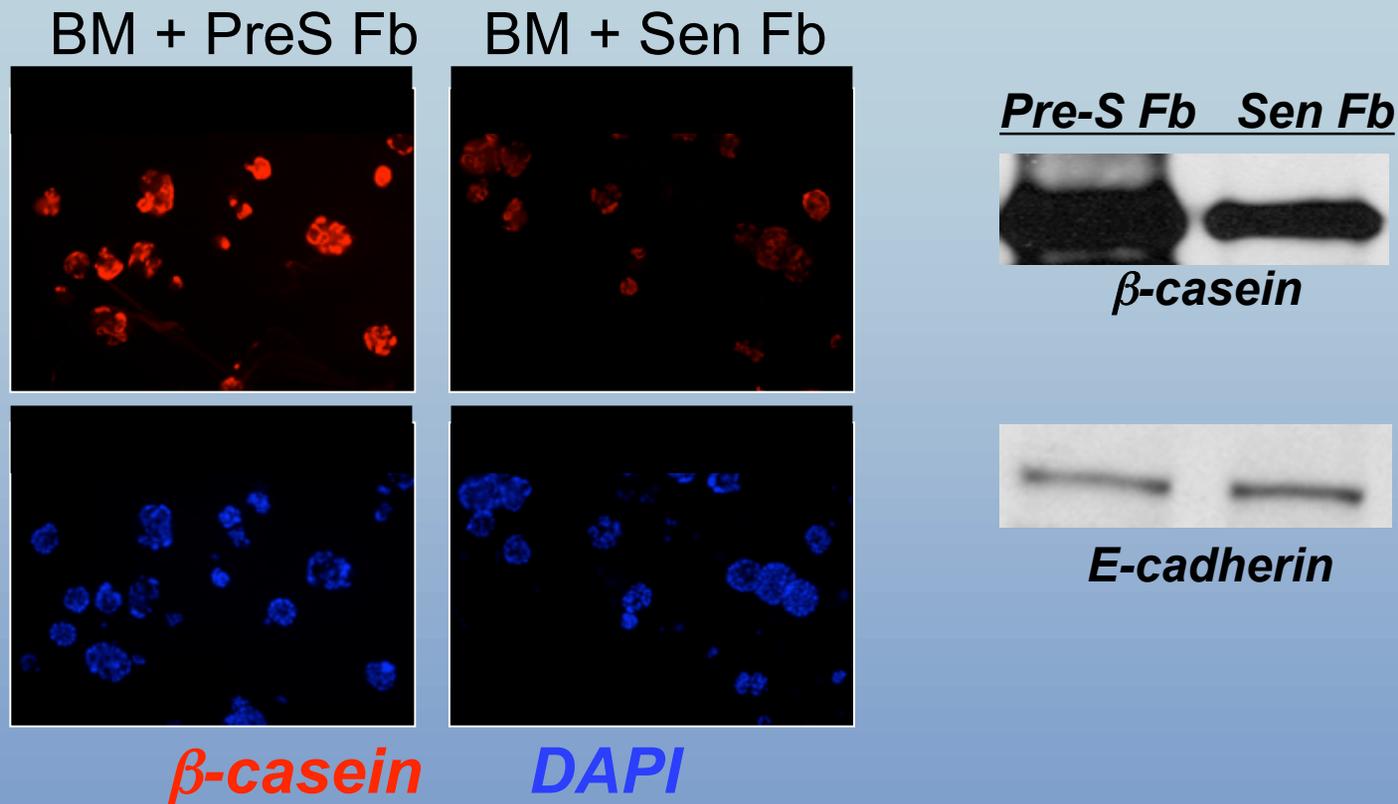


*Senescence-associated changes  
in gene expression:*

- Cell cycle regulation*
- Cell structure, metabolism*
- Secreted proteins with biological activity  
(inflammatory cytokines, proteases,  
growth factors)*

*Do senescent cells cause  
tissue degradation?*

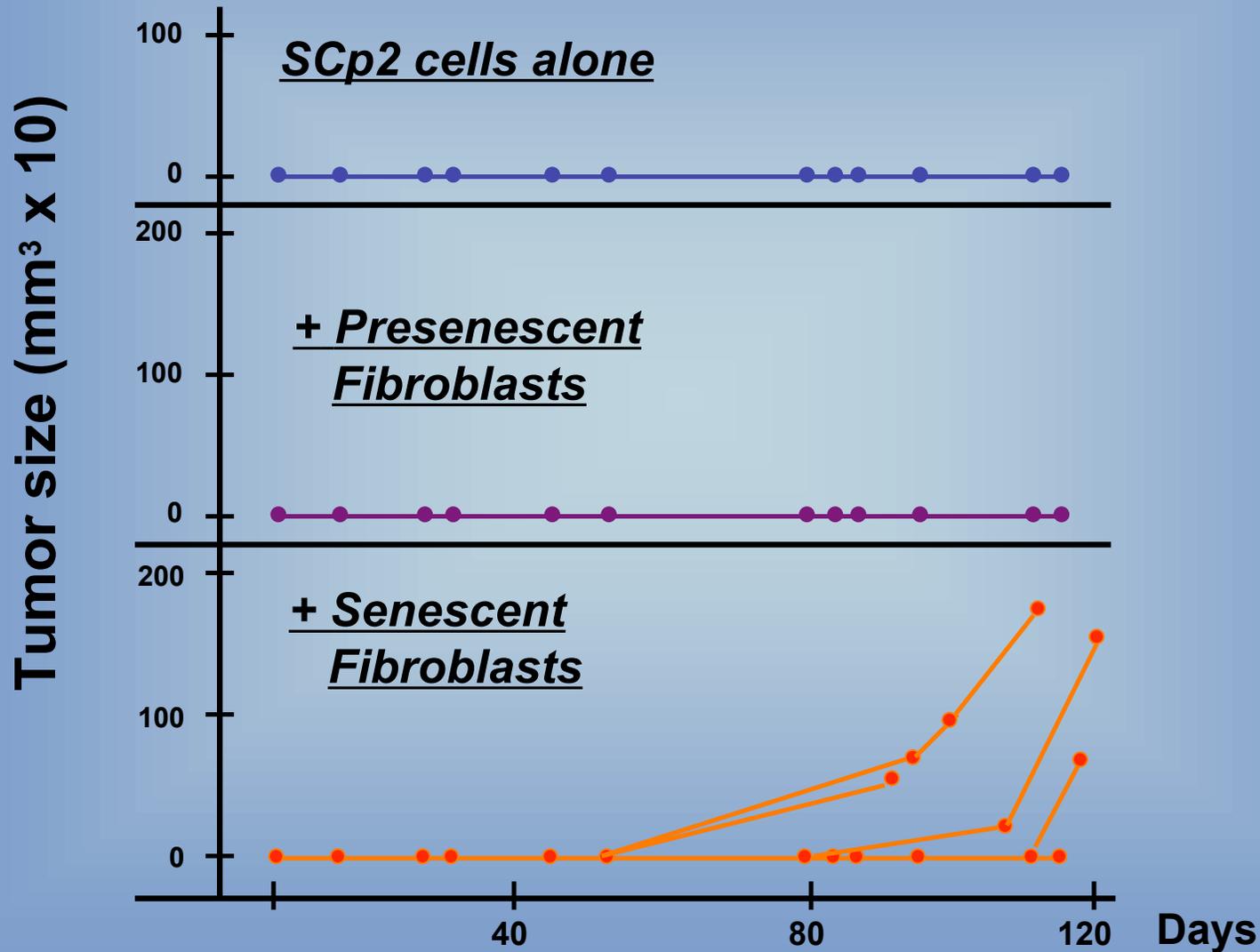
# *Senescent fibroblasts disrupt morphological and functional differentiation of mammary epithelial cells*



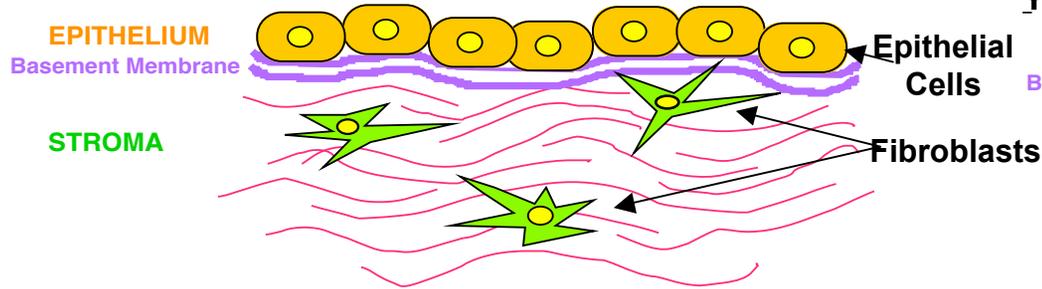
*If even young tissue contains mutant cells,  
and senescent cells cause tissue  
degradation.....*

*Might senescent cells promote cancer from  
nearby mutant cells???*

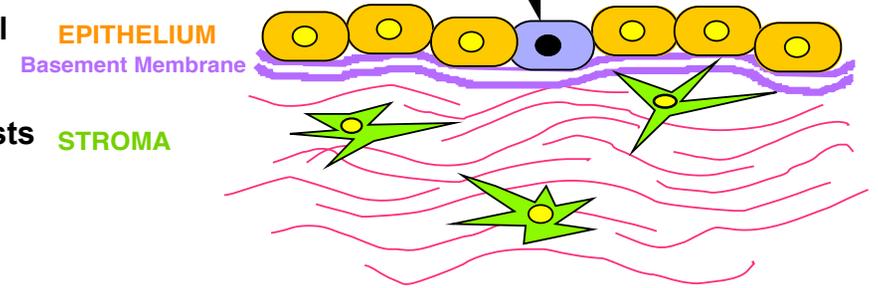
# Senescent Fibroblasts Stimulate Tumorigenesis of Premalignant Epithelial Cells In Vivo



**YOUNG TISSUE**

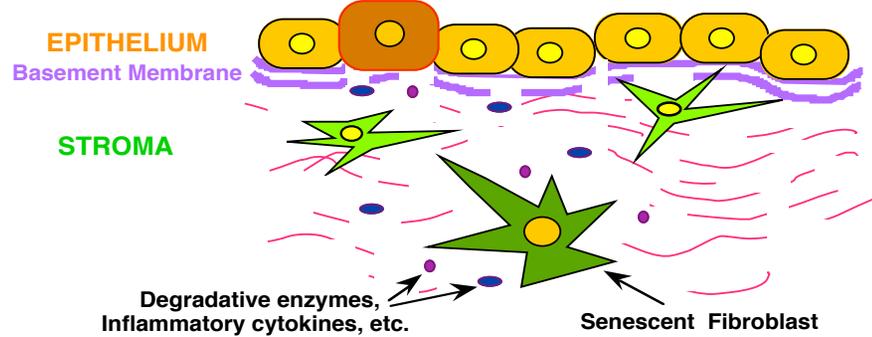


**YOUNG TISSUE**



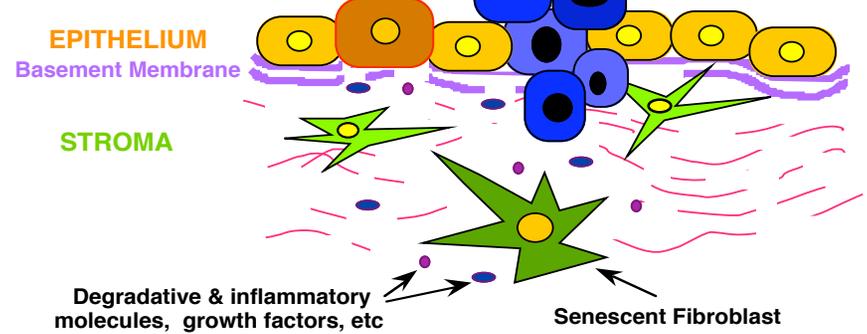
**AGING ?**

**OLD TISSUE**



**AGING ?**

**OLD TISSUE**



*What have learned?*

*The senescence growth arrest is good*

*The senescent secretory phenotype is bad  
(antagonistic pleiotropy)*

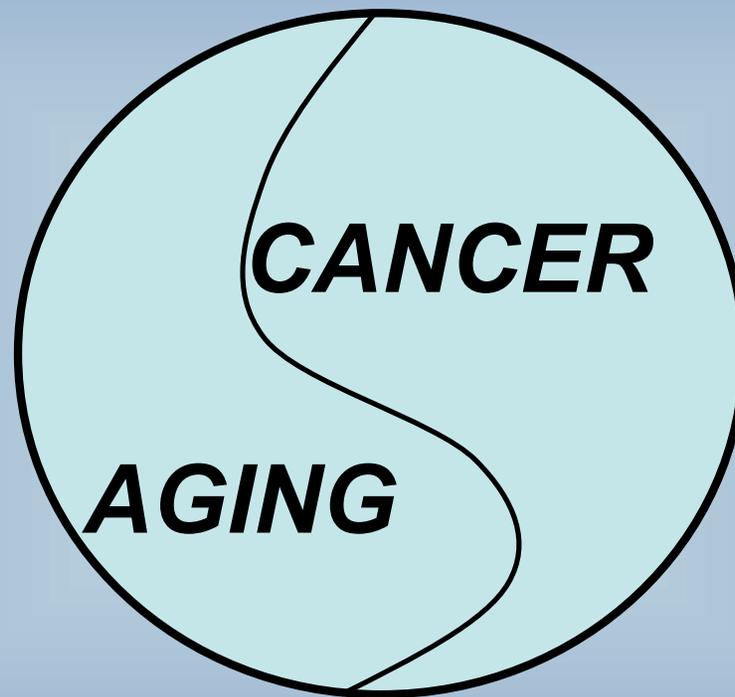
# *What is on the horizon?*

*Strategies to suppress senescent secretions  
without reversing the growth arrest*

*Strategies to eliminate senescent cells*

*(we're working on it!)*

*Aging and cancer are linked by the behavior of cells and forces of evolution*



*The 'solution'?*  
*Knowledge, knowledge, knowledge ....*  
*(and lot's of hard work!)*

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